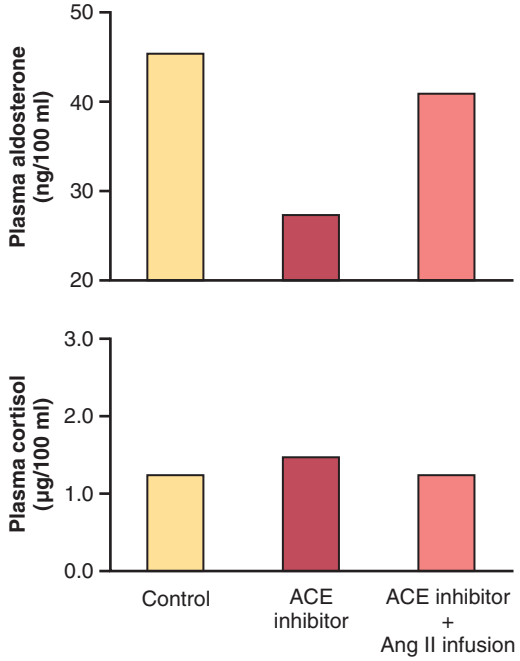


Figure 78-5. Effects of treating sodium-depleted dogs with an angiotensin-converting enzyme *(ACE)* inhibitor for 7 days to block formation of angiotensin II *(Ang II)* and of infusing exogenous Ang II to restore plasma Ang II levels after ACE inhibition. Note that blocking Ang II formation reduced plasma aldosterone concentration with little effect on cortisol, demonstrating the important role of Ang II in stimulating aldosterone secretion during sodium depletion. *(Data from Hall JE, Guyton AC, Smith MJ Jr, et al: Chronic blockade of angiotensin II formation during sodium deprivation. Am J Physiol 237:F424, 1979.)*

Chapters 28 and 30 for a more complete description of their functions.

Figure 78-5 shows the effects on plasma aldosterone concentration caused by blocking formation of angiotensin II with an angiotensin-converting enzyme inhibitor after several weeks of a low-sodium diet that increases plasma aldosterone concentration. Note that blockade of angiotensin II formation markedly decreases plasma aldosterone concentration without significantly changing cortisol concentration, which indicates the important role of angiotensin II in stimulating aldosterone secretion when sodium intake and extracellular fluid volume are reduced.

By contrast, the effects of sodium ion concentration per se and of ACTH in controlling aldosterone secretion are usually minor. Nevertheless, a 10 to 20 percent decrease in extracellular fluid sodium ion concentration, which occurs on rare occasions, can perhaps increase aldosterone secretion by about 50 percent. In the case of ACTH, if even a small amount is secreted by the anterior pituitary gland, it is usually enough to permit the adrenal glands to secrete whatever amount of aldosterone is required, but total absence of ACTH can significantly reduce aldosterone secretion. Therefore, ACTH appears to play a "permissive" role in regulation of aldosterone secretion.

FUNCTIONS OF GLUCOCORTICOIDS

Even though mineralocorticoids can save the life of an acutely adrenalectomized animal, the animal still is far from normal. Instead, the animal's metabolic systems for utilization of proteins, carbohydrates, and fats remain considerably deranged. Furthermore, the animal cannot resist different types of physical or even mental stress, and minor illnesses such as respiratory tract infections can lead to death. Therefore, the glucocorticoids have functions just as important to the long-continued life of the animal as those of the mineralocorticoids. These functions are explained in the following sections.

At least 95 percent of the glucocorticoid activity of the adrenocortical secretions results from the secretion of *cortisol,* known also as *hydrocortisone.* In addition, a small but significant amount of glucocorticoid activity is provided by *corticosterone.*

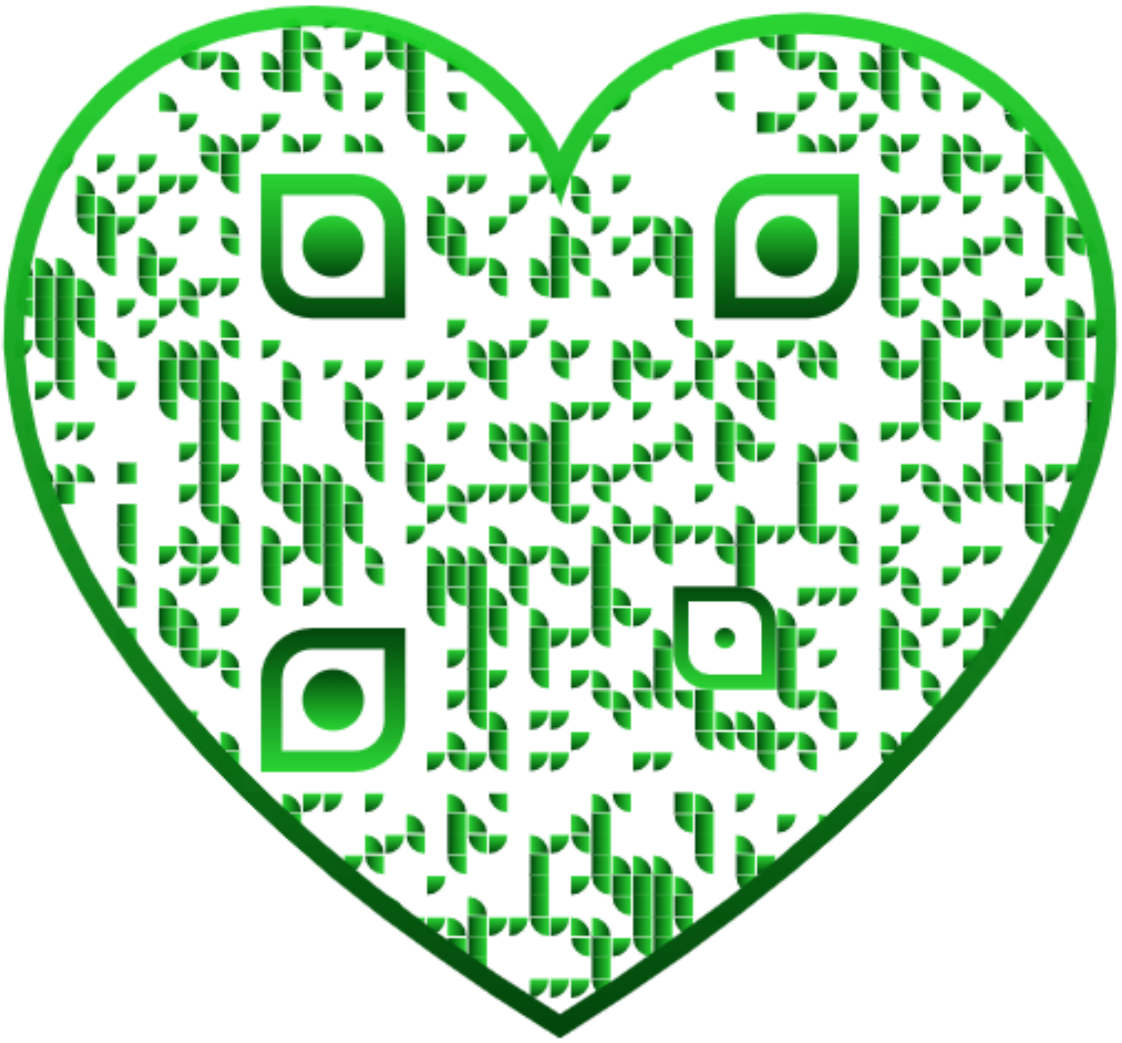
EFFECTS OF CORTISOL ON CARBOHYDRATE METABOLISM

Stimulation of Gluconeogenesis. The best-known metabolic effect of cortisol and other glucocorticoids on metabolism is the ability to stimulate gluconeogenesis (i.e., the formation of carbohydrate from proteins and some other substances) by the liver, often increasing the rate of gluconeogenesis as much as 6- to 10-fold. This increased rate of gluconeogenesis results mainly from direct effects of cortisol on the liver, as well as by antagonizing the effects of insulin.

1. *Cortisol increases the enzymes required to convert amino acids into glucose in liver cells.* This results from the effect of glucocorticoids to activate DNA transcription in the liver cell nuclei in the same way that aldosterone functions in renal tubular cells, with formation of mRNAs that in turn lead to the array of enzymes required for gluconeogenesis.
2. *Cortisol causes mobilization of amino acids from the extrahepatic tissues, mainly from muscle.* As a result, more amino acids become available in the plasma to enter into the gluconeogenesis process of the liver and thereby to promote the formation of glucose.
3. *Cortisol antagonizes insulin's effects to inhibit gluconeogenesis in the liver.* As discussed in Chapter 79, insulin stimulates glycogen synthesis in the liver and inhibits enzymes involved in glucose production by the liver. The net effect of cortisol is to increase glucose production by the liver.

The marked increase in glycogen storage in liver cells that accompanies increased gluconeogenesis potentiates the effects of other glycolytic hormones, such as epinephrine and glucagon, to mobilize glucose in times of need, such as between meals.

Decreased Glucose Utilization by Cells. Cortisol also causes a moderate decrease in glucose utilization by most



cells in the body. Although the precise cause of this decrease is unclear, one important effect of cortisol is to decrease translocation of the glucose transporters *GLUT 4* to the cell membrane, especially in skeletal muscle cells, leading to *insulin resistance*. Glucocorticoids may also depress the expression and phosphorylation of other signaling cascades that influence glucose utilization directly or indirectly by affecting protein and lipid metabolism. For example, glucocorticoids have been reported to reduce the expression of insulin receptor substrate–1 and phosphatidylinositol 3 kinase, both of which are involved in mediating the actions of insulin, as well as oxidation of nicotinamide-adenine dinucleotide (NADH) to form NAD^+. Because NADH must be oxidized to allow glycolysis, this effect could also contribute to diminished utilization of glucose by the cells.

Elevated Blood Glucose Concentration and "Adrenal Diabetes." Both the increased rate of gluconeogenesis and the moderate reduction in the rate of glucose utilization by the cells cause the blood glucose concentrations to rise. The rise in blood glucose in turn stimulates secretion of insulin. The increased plasma levels of insulin, however, are not as effective in maintaining plasma glucose as they are under normal conditions. For reasons that were discussed previously, high levels of glucocorticoid reduce the sensitivity of many tissues, especially skeletal muscle and adipose tissue, to the stimulatory effects of insulin on glucose uptake and utilization. Besides potential direct effects of cortisol on expression of glucose transporters and enzymes involved in glucose regulation, the high levels of fatty acids, caused by the effect of glucocorticoids to mobilize lipids from fat depots, may impair the actions of insulin on the tissues. In this way, excess secretion of glucocorticoids may produce disturbances of carbohydrate metabolism similar to those found in patients with excess levels of growth hormone.

The increase in blood glucose concentration is occasionally great enough (50 percent or more above normal) that the condition is called *adrenal diabetes.* Administration of insulin lowers the blood glucose concentration only a moderate amount in adrenal diabetes—not nearly as much as it does in pancreatic diabetes—because the tissues are resistant to the effects of insulin.

EFFECTS OF CORTISOL ON PROTEIN METABOLISM

Reduction in Cellular Protein. One of the principal effects of cortisol on the metabolic systems of the body is reduction of the protein stores in essentially all cells of the body except those of the liver. This reduction is caused by both decreased protein synthesis and increased catabolism of protein already in the cells. Both these effects may result partly from decreased amino acid transport into extrahepatic tissues, as discussed later, but this is probably not the major cause because cortisol also depresses the formation of RNA and subsequent protein synthesis in many extrahepatic tissues, especially in muscle and lymphoid tissue.

In the presence of great excesses of cortisol, the muscles can become so weak that the person cannot rise from the squatting position. In addition, the immunity functions of the lymphoid tissue can be decreased to a small fraction of normal.

Cortisol Increases Liver and Plasma Proteins. Coincidentally with the effect of glucocorticoids to reduce proteins elsewhere in the body, the liver proteins are increased. Furthermore, the plasma proteins (which are produced by the liver and then released into the blood) are also increased. These increases are exceptions to the protein depletion that occurs elsewhere in the body. It is believed that this difference results from a possible effect of cortisol to enhance amino acid transport into liver cells (but not into most other cells) and to enhance the liver enzymes required for protein synthesis.

Increased Blood Amino Acids, Diminished Transport of Amino Acids Into Extrahepatic Cells, and Enhanced Transport Into Hepatic Cells. Studies in isolated tissues have demonstrated that cortisol depresses amino acid transport into muscle cells and perhaps into other extrahepatic cells.

The decreased transport of amino acids into extrahepatic cells decreases their intracellular amino acid concentrations and consequently decreases the synthesis of protein. Yet, catabolism of proteins in the cells continues to release amino acids that diffuse out of the cells to increase the plasma amino acid concentration. Therefore, *cortisol mobilizes amino acids from the nonhepatic tissues* and in doing so diminishes the tissue stores of protein.

The increased plasma concentration of amino acids and enhanced transport of amino acids into the hepatic cells by cortisol could also account for enhanced utilization of amino acids by the liver to cause such effects as (1) increased rate of deamination of amino acids by the liver, (2) increased protein synthesis in the liver, (3) increased formation of plasma proteins by the liver, and (4) increased conversion of amino acids to glucose—that is, enhanced gluconeogenesis. Thus, it is possible that many of the effects of cortisol on the metabolic systems of the body result mainly from this ability of cortisol to mobilize amino acids from the peripheral tissues while at the same time increasing the liver enzymes required for the hepatic effects.

EFFECTS OF CORTISOL ON FAT METABOLISM

Mobilization of Fatty Acids. In much the same manner that cortisol promotes amino acid mobilization from muscle, it also promotes mobilization of fatty acids from adipose tissue. This mobilization increases the

concentration of free fatty acids in the plasma, which also increases their utilization for energy. Cortisol also seems to have a direct effect to enhance the oxidation of fatty acids in the cells.

The mechanism by which cortisol promotes fatty acid mobilization is not completely understood. However, part of the effect probably results from diminished transport of glucose into the fat cells. Recall that α-glycerophosphate, which is derived from glucose, is required for both deposition and maintenance of triglycerides in these cells. In its absence, the fat cells begin to release fatty acids.

The increased mobilization of fats by cortisol, combined with increased oxidation of fatty acids in the cells, helps shift the metabolic systems of the cells from utilization of glucose for energy to utilization of fatty acids in times of starvation or other stresses. This cortisol mechanism, however, requires several hours to become fully developed—not nearly so rapid or so powerful an effect as a similar shift elicited by a decrease in insulin, as we discuss in Chapter 79. Nevertheless, the increased use of fatty acids for metabolic energy is an important factor for long-term conservation of body glucose and glycogen.

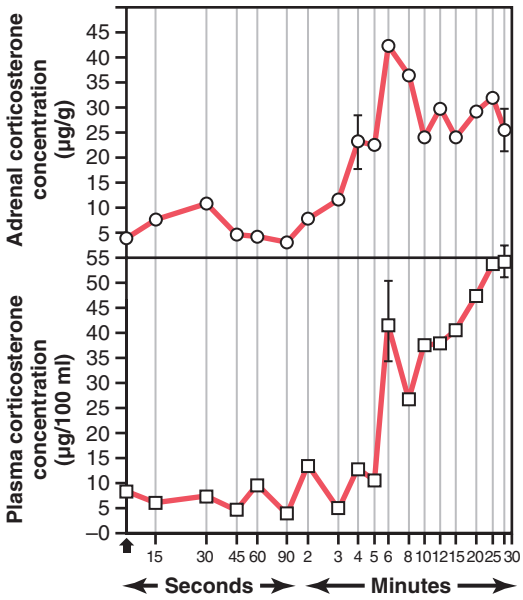


Figure 78-6. Rapid reaction of the adrenal cortex of a rat to stress caused by fracture of the tibia and fibula at time zero. (In the rat, corticosterone is secreted in place of cortisol.)

Excess Cortisol Causes Obesity. Despite the fact that cortisol can cause a moderate degree of fatty acid mobilization from adipose tissue, a peculiar type of obesity develops in many people with excess cortisol secretion, with excess deposition of fat in the chest and head regions of the body, giving a buffalo-like torso and a rounded "moon face." Although the cause is unclear, it has been suggested that this obesity results from excess stimulation of food intake, with fat being generated in some tissues of the body more rapidly than it is mobilized and oxidized.

CORTISOL IS IMPORTANT IN RESISTING STRESS AND INFLAMMATION

Almost any type of stress, whether physical or neurogenic, causes an immediate and marked increase in ACTH secretion by the anterior pituitary gland, followed within minutes by greatly increased adrenocortical secretion of cortisol. This effect is demonstrated dramatically by the experiment shown in **Figure 78-6**, in which corticosteroid formation and secretion increased sixfold in a rat within 4 to 20 minutes after fracture of two leg bones.

The following list details some of the different types of stress that increase cortisol release:

1. Trauma
2. Infection
3. Intense heat or cold
4. Injection of norepinephrine and other sympathomimetic drugs
5. Surgery
6. Injection of necrotizing substances beneath the skin
7. Restraining an animal so it cannot move
8. Debilitating diseases

Even though cortisol secretion often increases greatly in stressful situations, we are not sure why this is of significant benefit to the animal. One possibility is that the glucocorticoids cause rapid mobilization of amino acids and fats from their cellular stores, making them immediately available both for energy and for synthesis of other compounds, including glucose, needed by the different tissues of the body. Indeed, it has been shown in a few instances that damaged tissues that are momentarily depleted of proteins can use the newly available amino acids to form new proteins that are essential to the lives of the cells. Also, the amino acids are perhaps used to synthesize other essential intracellular substances, such as purines, pyrimidines, and creatine phosphate, which are necessary for maintenance of cellular life and reproduction of new cells.

All this is mainly supposition and is supported only by the fact that cortisol usually does not mobilize the basic functional proteins of the cells, such as the muscle contractile proteins and the proteins of neurons, until almost all other proteins have been released. This preferential effect of cortisol in mobilizing labile proteins could make amino acids available to needy cells to synthesize substances essential to life.

Anti-inflammatory Effects of High Levels of Cortisol

When tissues are damaged by trauma, by infection with bacteria, or in other ways, they almost always become "inflamed." In some conditions, such as in rheumatoid arthritis, the inflammation is more damaging than the trauma or disease itself. Administration of large amounts of cortisol can usually block this inflammation or even reverse many of its effects once it has begun. Before

attempting to explain the way in which cortisol functions to block inflammation, let us review the basic steps in the inflammation process, which are discussed in more detail in Chapter 34.

Five main stages of inflammation occur: (1) release from the damaged tissue cells of chemicals such as histamine, bradykinin, proteolytic enzymes, prostaglandins, and leukotrienes that activate the inflammation process; (2) an increase in blood flow in the inflamed area caused by some of the released products from the tissues, an effect called *erythema;* (3) leakage of large quantities of almost pure plasma out of the capillaries into the damaged areas because of increased capillary permeability, followed by clotting of the tissue fluid, thus causing a *nonpitting type of edema;* (4) infiltration of the area by leukocytes; and (5) after days or weeks, ingrowth of fibrous tissue that often helps in the healing process.

When large amounts of cortisol are secreted or injected into a person, the glucocorticoid has two basic *anti-inflammatory effects:* (1) it can block the early stages of the inflammation process before noticeable inflammation even begins, or (2) if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing. These effects are explained further in the following sections.

Cortisol Prevents the Development of Inflammation by Stabilizing Lysosomes and by Other Effects. Cortisol has the following effects in preventing inflammation:

1. *Cortisol stabilizes lysosomal membranes.* This stabilization is one of its most important anti-inflammatory effects because it is much more difficult than normal for the membranes of the intracellular lysosomes to rupture. Therefore, most of the proteolytic enzymes that are released by damaged cells to cause inflammation, which are mainly stored in the lysosomes, are released in greatly decreased quantities.
2. *Cortisol decreases permeability of the capillaries,* probably as a secondary effect of the reduced release of proteolytic enzymes. This decrease in permeability prevents loss of plasma into the tissues.
3. *Cortisol decreases both migration of white blood cells into the inflamed area and phagocytosis of the damaged cells.* These effects probably result from the fact that cortisol diminishes formation of prostaglandins and leukotrienes that otherwise would increase vasodilation, capillary permeability, and mobility of white blood cells.
4. *Cortisol suppresses the immune system, causing lymphocyte reproduction to decrease markedly.* The T lymphocytes are especially suppressed. In turn, reduced amounts of T cells and antibodies in the inflamed area lessen tissue reactions that would otherwise promote inflammation.
5. *Cortisol attenuates fever mainly because it reduces release of interleukin-1 from white blood cells,* which is one of the principal excitants to the hypothalamic temperature control system. The decreased temperature in turn reduces the degree of vasodilation.

Thus, cortisol has an almost global effect in reducing all aspects of the inflammatory process. It is unclear how much of this reduction results from the simple effect of cortisol in stabilizing lysosomal and cell membranes versus its effect in reducing the formation of prostaglandins and leukotrienes from arachidonic acid in damaged cell membranes and other effects of cortisol.

Cortisol Causes Resolution of Inflammation. Even after inflammation has become well established, administration of cortisol can often reduce inflammation within hours to a few days. The immediate effect is to block most of the factors that promote the inflammation. In addition, however, the rate of healing is enhanced. This probably results from the same, mainly undefined, factors that allow the body to resist many other types of physical stress when large quantities of cortisol are secreted. Perhaps this results from (1) the mobilization of amino acids and use of these acids to repair the damaged tissues; (2) the increased glucogenesis that makes extra glucose available in critical metabolic systems; (3) increased amounts of fatty acids available for cellular energy; or (4) some effect of cortisol for inactivating or removing inflammatory products.

Regardless of the precise mechanisms by which the anti-inflammatory effect occurs, this effect of cortisol plays a major role in combating certain types of diseases, such as rheumatoid arthritis, rheumatic fever, and acute glomerulonephritis. All these diseases are characterized by severe local inflammation, and the harmful effects on the body are caused mainly by the inflammation and not by other aspects of the disease.

When cortisol or other glucocorticoids are administered to patients with these diseases, almost invariably the inflammation begins to subside within 24 hours. Even though the cortisol does not correct the basic disease condition, preventing the damaging effects of the inflammatory response can often be a lifesaving measure.

Other Effects of Cortisol

Cortisol Blocks the Inflammatory Response to Allergic Reactions. The basic allergic reaction between antigen and antibody is not affected by cortisol, and even some of the secondary effects of the allergic reaction still occur. However, because the inflammatory response is responsible for many of the serious and sometimes lethal effects of allergic reactions, administration of cortisol, followed by its effect in reducing inflammation and the release of inflammatory products, can be lifesaving. For instance, cortisol effectively prevents shock or death as a result of anaphylaxis, a condition that otherwise kills many people, as explained in Chapter 35.

Effect on Blood Cells and on Immunity in Infectious Diseases. Cortisol decreases the number of eosinophils and lymphocytes in the blood; this effect begins within a few minutes after the injection of cortisol and becomes marked within a few hours. Indeed, a finding of lymphocytopenia or eosinopenia is an important diagnostic criterion for overproduction of cortisol by the adrenal gland.

Likewise, administration of large doses of cortisol causes significant atrophy of lymphoid tissue throughout the body, which in turn decreases the output of T cells and antibodies from the lymphoid tissue. As a result, the level of immunity for almost all foreign invaders of the body is decreased. This decrease occasionally can lead to fulminating infection and death from diseases that would otherwise not be lethal, such as fulminating tuberculosis in a person whose disease had previously been arrested. However, this ability of cortisol and other glucocorticoids to suppress immunity makes them useful drugs in preventing immunological rejection of transplanted hearts, kidneys, and other tissues.

Cortisol increases the production of red blood cells by mechanisms that are unclear. When excess cortisol is secreted by the adrenal glands, polycythemia often results, and conversely, when the adrenal glands secrete no cortisol, anemia often results.

Cellular Mechanism of Cortisol Action

Cortisol, like other steroid hormones, exerts its effects by first interacting with intracellular receptors in target cells. Because cortisol is lipid soluble, it can easily diffuse through the cell membrane. Once inside the cell, cortisol binds with its protein receptor in the cytoplasm, and the hormone-receptor complex then interacts with specific regulatory DNA sequences, called *glucocorticoid response elements,* to induce or repress gene transcription. Other proteins in the cell, called *transcription factors,* are also necessary for the hormone-receptor complex to interact appropriately with the glucocorticoid response elements.

Glucocorticoids increase or decrease transcription of many genes to alter synthesis of mRNA for the proteins that mediate their multiple physiological effects. Thus, most of the metabolic effects of cortisol are not immediate but require 45 to 60 minutes for proteins to be synthesized, and up to several hours or days to fully develop. Recent evidence suggests that glucocorticoids, especially at high concentrations, may also have some rapid *nongenomic effects* on cell membrane ion transport that may contribute to their therapeutic benefits.

REGULATION OF CORTISOL SECRETION BY ADRENOCORTICOTROPIC HORMONE FROM THE PITUITARY GLAND

ACTH Stimulates Cortisol Secretion. Unlike aldosterone secretion by the zona glomerulosa, which is controlled mainly by potassium and angiotensin II acting directly on the adrenocortical cells, secretion of cortisol is controlled almost entirely by ACTH that is secreted by the anterior pituitary gland. This hormone, also called *corticotropin* or *adrenocorticotropin,* also enhances the production of adrenal androgens.

Chemistry of ACTH. ACTH has been isolated in pure form from the anterior pituitary. It is a large polypeptide, having a chain length of 39 amino acids. A smaller polypeptide, a digested product of ACTH having a chain length of 24 amino acids, has all the effects of the total molecule.

ACTH Secretion Is Controlled by Corticotropin-Releasing Factor From the Hypothalamus. In the same way that other pituitary hormones are controlled by releasing factors from the hypothalamus, an important releasing factor also controls ACTH secretion. This factor is called *corticotropin-releasing factor* (CRF). It is secreted into the primary capillary plexus of the hypophysial portal system in the median eminence of the hypothalamus and then carried to the anterior pituitary gland, where it induces ACTH secretion. CRF is a peptide composed of 41 amino acids. The cell bodies of the neurons that secrete CRF are located mainly in the paraventricular nucleus of the hypothalamus. This nucleus in turn receives many nervous connections from the limbic system and lower brain stem.

The anterior pituitary gland can secrete only minute quantities of ACTH in the absence of CRF. Instead, most conditions that cause high ACTH secretory rates initiate this secretion by signals that begin in the basal regions of the brain, including the hypothalamus, and are then transmitted by CRF to the anterior pituitary gland.

ACTH Activates Adrenocortical Cells to Produce Steroids by Increasing cAMP. The principal effect of ACTH on the adrenocortical cells is to activate *adenylyl cyclase* in the cell membrane. This activation then induces the formation of *cAMP* in the cell cytoplasm, reaching its maximal effect in about 3 minutes. The cAMP in turn activates the intracellular enzymes that cause formation of the adrenocortical hormones, which is another example of cAMP as a *second messenger* signal system.

The most important of all the ACTH-stimulated steps for controlling adrenocortical secretion is activation of the enzyme *protein kinase A,* which *causes initial conversion of cholesterol to pregnenolone.* This initial conversion is the "rate-limiting" step for all the adrenocortical hormones, which explains why ACTH is normally necessary for any adrenocortical hormones to be formed. Long-term stimulation of the adrenal cortex by ACTH not only increases secretory activity but also causes hypertrophy and proliferation of the adrenocortical cells, especially in the zona fasciculata and zona reticularis, where cortisol and the androgens are secreted.

Physiological Stress Increases ACTH and Adrenocortical Secretion. As pointed out earlier in the

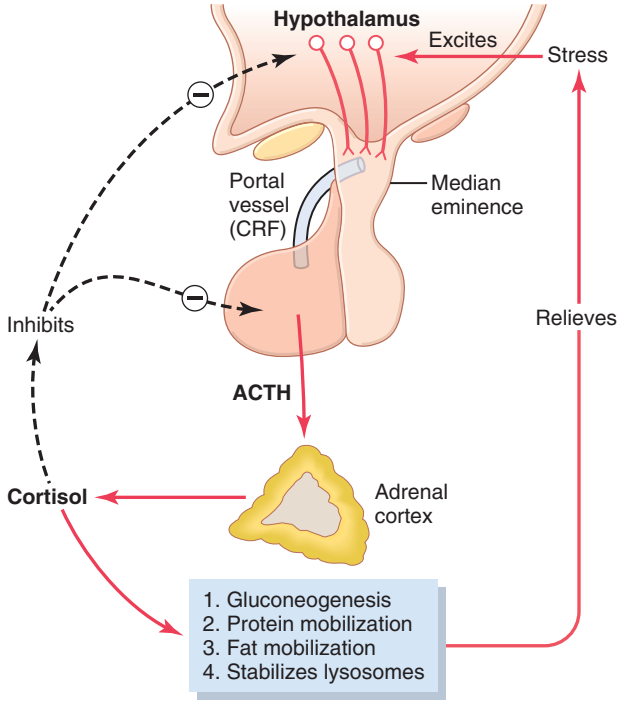


Figure 78-7. Mechanism for regulation of glucocorticoid secretion. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor.

chapter, almost any type of physical or mental stress can lead within minutes to greatly enhanced secretion of ACTH and consequently cortisol as well, often increasing cortisol secretion as much as 20-fold. This effect was demonstrated by the rapid and strong adrenocortical secretory responses after trauma shown in Figure 78-6.

Pain stimuli caused by physical stress or tissue damage are transmitted first upward through the brain stem and eventually to the median eminence of the hypothalamus, as shown in Figure 78-7. Here CRF is secreted into the hypophysial portal system. Within minutes the entire control sequence leads to large quantities of cortisol in the blood.

Mental stress can cause an equally rapid increase in ACTH secretion. This increase is believed to result from increased activity in the limbic system, especially in the region of the amygdala and hippocampus, both of which then transmit signals to the posterior medial hypothalamus.

Inhibitory Effect of Cortisol on the Hypothalamus and on the Anterior Pituitary to Decrease ACTH Secretion. Cortisol has direct negative feedback effects on (1) the hypothalamus to decrease the formation of CRF and (2) the anterior pituitary gland to decrease the formation of ACTH. Both of these feedbacks help regulate the plasma concentration of cortisol. That is, whenever the cortisol concentration becomes too great, the feedbacks automatically reduce the ACTH toward a normal control level.

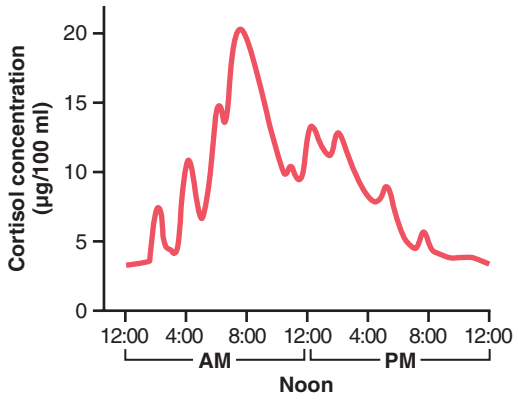


Figure 78-8. Typical pattern of cortisol concentration during the day. Note the oscillations in secretion, as well as a daily secretory surge an hour or so after waking in the morning.

Summary of the Cortisol Control System

Figure 78-7 shows the overall system for control of cortisol secretion. The key to this control is the excitation of the hypothalamus by different types of stress. Stress stimuli activate the entire system to cause rapid release of cortisol, and the cortisol in turn initiates a series of metabolic effects directed toward relieving the damaging nature of the stressful state.

Direct feedback of the cortisol to both the hypothalamus and the anterior pituitary gland also occurs to decrease the concentration of cortisol in the plasma at times when the body is not experiencing stress. However, the stress stimuli are the most potent ones; they can always break through this direct inhibitory feedback of cortisol, causing either periodic exacerbations of cortisol secretion at multiple times during the day (Figure 78-8) or prolonged cortisol secretion in times of chronic stress.

Circadian Rhythm of Glucocorticoid Secretion. The secretory rates of CRF, ACTH, and cortisol are high in the early morning but low in the late evening, as shown in Figure 78-8; the plasma cortisol level ranges between a high of about 20 µg/dl an hour before arising in the morning and a low of about 5 µg/dl around midnight. This effect results from a 24-hour cyclical alteration in the signals from the hypothalamus that cause cortisol secretion. When a person changes daily sleeping habits, the cycle changes correspondingly. Therefore, measurements of blood cortisol levels are meaningful only when expressed in terms of the time in the cycle at which the measurements are made.

Synthesis and Secretion of ACTH in Association with Melanocyte-Stimulating Hormone, Lipotropin, and Endorphin

When ACTH is secreted by the anterior pituitary gland, several other hormones that have similar chemical structures are secreted simultaneously. The reason for this